jc714 U.S. PTO
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03-02-00

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Attorney Docket No. 45061-8

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

Inventor(s) : Zsolt I. Hertelendy
Murray Weiner
Michael Howell
Joseph Thomas

For (title) : UROGENTIAL OR ANORECTAL TRANSMUCOSAL VACCINE DELIVERY SYSTEM

1. Type of Application

This new application is for a(n):

(X) Original (nonprovisional)
( ) Continuation
( ) Continuation-in-part (CIP)
( ) Divisional
( ) Design
( ) Plant

CERTIFICATION UNDER 37 C.F.R. 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this New Application Transmittal and the documents referred to as attached therein are being deposited with the United States Postal Service on this date March 1, 2000, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number EM016592972US addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Antoinette P. Wolas
(type or print name of person mailing paper)

Antoinette P Wolas
Signature of person mailing paper

2. Benefit of Prior U.S. Application(s) (35 U.S.C. 119(e), 120, or 121)

[ ] The new application being transmitted claims the benefit of prior U.S. application(s).

2.1 Relate Back

Amend the specification by inserting, before the first line, the following sentence:

A. 35 U.S.C. 120, 121 and 365(c)

() "This is a
( ) continuation
( ) continuation-in-part
( ) divisional

of copending application(s) serial number filed on ."

( ) International Application_____ filed on_____ and which designated the U.S."

( ) "The nonprovisional application designated above, namely application no._____, filed_____, claims the benefit of U.S. Provisional Application(s) No(s).:

{list application no(s). and filing date(s)}

B. 35 U.S.C. 119(e) (Provisional Application)

( ) "This application claims the benefit of U.S. Provisional Application(s) No(s).:

2.2 Relate Back—35 U.S.C. 119 Priority Claim for Prior Application

The prior U.S. application(s), including any prior International Application designating the U.S., identified above in item 2.1(A), in turn itself claim(s) foreign priority(ies) as follows:

{list country, application no(s). and filing date(s)}

The certified copy(ies) has (have)

( ) been filed on_____, in prior application serial no.____, which was filed on___.

( ) is (are) attached.

2.3 Maintenance of Copendency of Prior Application

A. ( ) Extension of time in prior application

( ) A petition, fee and response extends the term in the pending **prior** application until Extension of_____.

( ) A **copy** of the petition filed in prior application is attached.

B. ( ) Conditional Petition for Extension of Time in Prior Application

( ) A conditional petition for extension of time is being filed in the pending **prior** application.

( ) A **copy** of the conditional petition filed in the prior application is attached.

2.4 Further Inventorship Statement Where Benefit of Prior Application(s) Claimed

A. ( ) This application discloses and claims only subject matter disclosed in the prior application whose particulars are set out above and the inventor(s) In this application are

( ) the same.

( ) less than those named in the prior application. It is requested that the following inventor(s) identified for the prior application be deleted:

B. ( ) This application discloses and claims additional disclosure by amendment and a new declaration or oath is being filed. With respect to the prior application, the inventor(s) in this application are

( ) the same.

( ) the following additional inventor(s) have been added:

C. **(X)** The inventorship for all the claims in this application are

(X) the same.

() not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made

( ) is submitted.

( ) will be submitted.

2.5 Abandonment of Prior Application *(if applicable)*

( ) Please abandon the prior application at a time while the prior application is pending, or when the petition for extension of time or to revive In that application is granted, and when this application is granted a filing date, so to make this application copending with said prior application.

2.6 Petition for Suspension of Prosecution for the Time Necessary to File an Amendment

( ) There is provided herewith a Petition To Suspend Prosecution for the Time Necessary to File An Amendment (New Application Filed Concurrently)

2.7 Small Entity (37 CFR § 1.28(a))

( ) Applicant has established small entity status by the previous submission of a statement in prior application serial no.

(X) A copy of the statement is included.

2.8. Notification in Parent Application of this Filing

( ) A notification of the filing of this

( ) continuation
( ) continuation-in-part
( ) divisional
is being filed in the parent application, from which this application claims priority under 35 U.S.C. § 120.

2.9 Incorporation by Reference

() the entire disclosure of the prior application, from which a copy of the oath or declaration is supplied, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

3. Papers Enclosed Which are Required for Filing Date Under 37 CFR 1.53(b) (Regular) or 37 CFR 1.153 (Design) Application

(X) 16 Pages of specification
(X) 7 Pages of claims
(X) 1 Pages of Abstract
() _ Sheets of drawing
() formal
() informal

4. Additional papers enclosed

() Amendment to claims:

( ) **Cancel** in this application claims_____ before calculating the filing fee. (At least one original independent claim must be retained for filing purposes).

( ) **Add** the claims shown in the attached amendment. (Claims added have been numbered consecutively following the highest numbered original claims).

( ) Preliminary Amendment
( ) Information Disclosure Statement (37 C.F.R. 1.98)
() Form PTO-1449
() References
( ) Declaration of Biological Deposit
( ) Special Comments
( ) Other

5. Declaration or oath (including power of attorney)

(X) ENCLOSED.
() Newly executed (original or copy)
() Copy from prior application No. 0 /_____ (37 CFR 1.63(d)- continuation/divisional)

( ) DELETION OF INVENTOR(S) - signed statement attached deleting inventor(s) named in the above-noted prior application (37 CFR 1.63(d) and 1.33(b))

Declaration or Oath executed by: (check **all** applicable boxes)
(X) inventor(s).
( ) legal representative of inventor(s). 37 CFR 1.42 or 1.43
( ) joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.
( ) this is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. See item 13 below for fee.

() NOT ENCLOSED.
() Application is made by a person authorized under 37 CFR 1.41(c) on behalf of all the above named inventor(s). The declaration or oath, along with the surcharge required by 37 CFR 1.16(e) can be filed subsequently.
( ) Showing that the filing is authorized. (Not required unless called into question. 37 CFR 1.41(d)).

6. Inventorship Statement

() The inventorship for all the claims in this application are:
(X) The same

or

() Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,
- () is submitted
- () will be submitted.

7. Language

(X) English
() Non-English
() the attached translation is a verified translation. 37 CFR 1.52(d).

8. Assignment

(X) An assignment of the invention to Protein Express

- (X) is attached. (A separate "ASSIGNMENT COVER LETTER ACCOMPANYING NEW PATENT APPLICATION" is also attached.)
- () will follow.

() The prior application is assigned of record to_____copy attached).

9. Certified Copy - Foreign Priority Claim Under 35 U.S.C. 119

Certified copy(ies) of application(s)

{list country, application no(s). and filing date(s)}

from which priority is claimed
- () is (are) attached.
- () will follow.

10. Fee Calculation (37 C.F.R. 1.16)

A. (X) Regular Application

CLAIMS AS FILED				
	Number Filed	Number Extra	Rate	Basic Fee $345.00
Total Claims (37 CFR 1.16(c))	20 - 20 =	0	x $18.00	$0.00
Independent Claims (37 CFR 1.16(b))	6 - 3 =	3	x $78.00	$224.00
Multiple dependent claim(s), if any (37 CFR 1.16(d))	0	0	x $260.00	$ 0.00

( ) Amendment canceling extra claims enclosed.
( ) Amendment deleting multiple dependencies enclosed.
( ) Fee for extra claims is not being paid at this time.

Filing Fee Calculation $569.00

B. () Design Application
($330.00 - 37 CFR 1.16(f))

Filing Fee Calculation $

11. Small Entity Statement(s)

(X) Verified Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is(are) attached.

12. Request for International-Type Search (37 C.F.R. 1.104(d))

( ) Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

13. Fee Payment Being Made At This Time

( ) NOT ENCLOSED.
( ) No filing fee is to be paid at this time. (This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.)

(X) ENCLOSED
(X) Filing fee $ 569.00

(X) Recording assignment
($40.00; 37 CFR 1.21(h)(1)) $ 40.00

( ) petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached. ($130.00; 37 CFR 1.47 & 1.17(h))
$_____

( ) for processing an application with a specification is a non-English language. ($130.00 37 CFR 1.52(d) and 1.17(k))
$_____

( ) processing and retention fee. ($130.00; 37 CFR 1.53(d) and 1.21(l))
$_____

( ) Fee for international-type search report. ($40.00; 37 CFR 1.21(e))
$_____

Total fees enclosed **$609.00**

14. Method of Payment of Fees

(X) Check in the amount of $609.00

0 Charge **Account No. 02-2051** in the amount of **$0** A duplicate of this transmittal is attached.

15. Authorization to Charge Additional Fees

(X) The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. 02-2051, **identifying our Attorney Docket No. 45061-8**

(X) 37 CFR 1.16(a), (f), or (g) (filing fees)
(X) 37 CFR 1.16(b), (c) and (d) (presentation of extra claims)
(X) 37 CFR 1.17 (application processing fees)
( ) 37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)
( ) 37 CFR 1.17(a)(1)-(5) (extension fees pursuant to 37 CFR 1.136(a))

( ) 37 CFR 1.18 (issue fee at or before mailing Notice of Allowance, pursuant to 37 CFR 1.311(b))

16. Instruction As To Overpayment

(X) Credit Account No. 02-2051, **identifying our Attorney Docket No. 45061-8**
( ) Refund

17. Incorporation by reference of added pages

() The following pages are incorporated by reference:

(X) "Assignment Cover Letter Accompanying New Application"; number of pages added

() Added Pages For Papers Referred To In Item 4 Above; number of pages added

( ) Plus added pages deleting names of inventor(s) named in prior application(s) who is/are no longer inventor(s) of the subject matter claimed in this application; number of pages added_____.

(X) no further pages form a part of this Transmittal. The transmittal ends with this page.

Date: 3/1/00

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	:	Hertelendy, et al.
FOR	:	UROGENITAL OR ANORECTAL TRANSMUCOSAL VACCINE DELIVERY SYSTEM
ATTORNEY DOCKET NO.	:	45061-8
		Cleveland, Ohio 44114-2378

37 C.F.R. 1.27
STATEMENT OF STATUS AS
A SMALL BUSINESS ENTITY

Assistant Commissioner For Patents
Washington, DC 20231

Dear Sir:

The undersigned affirms:

That he is an officer of the assignee Protein Express, and is empowered to act on behalf of the assignee; the assignment is being filed concurrently herewith for recording;

That the assignee Protein Express, together with all of its affiliates combined had fewer than five hundred (500) employees including full-time, part-time, and temporary employees on the average during each pay period of the previous fiscal year of the assignee and its affiliates; and,

That the assignee has not assigned, granted, conveyed, or licensed, and is under no obligation under contract or law to assign, grant, convey, or license any rights in the invention to any person who could not be classified as an independent inventor under 37 C.F.R. 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business under 37 C.F.R. 1.9(d) or a nonprofit organization under 37 C.F.R. 1.9(e).

The undersigned acknowledges a duty to file, in this application or patents issuing thereon, notification of any change in status resulting in loss of entitlement to small entity status

prior to paying, or at the time or paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful and false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2-24-99

By: _____
Name: ZSOLT HERTELENDY
Title: Treasurer

Atty. Docket: 45061-8

UROGENITAL OR ANORECTAL TRANSMUCOSAL VACCINE DELIVERY SYSTEM

Field of Invention

The present invention relates generally to a system and method for treating disease in humans and animals, specifically a prophylactic treatment of viral or microbial infections in humans or animals. More particularly, the invention relates to a suppository-based, vaccine delivery system for prophylaxis against or therapy for viral or microbial infections in humans or animals, wherein the suppository is intended for transmucosal immunization and is comprised of a vaccine or vaccine adjuvant(s) that is derived from whole or fractionated viral or other microbial pathogens, or their purified cellular constituents or derivatives, whether native, synthetic, cloned or recombinantly expressed, that consists of nucleotide sequences, proteins or other antigenic determinants capable of producing humoral or cellular-mediated immunity in humans or animals. Still more particularly, the present invention relates to a suppository-based, vaccine delivery system for prophylaxis against or therapy for viral or microbial infections in humans or animals, wherein the suppository is used for transmucosal immunization and is comprised of a vaccine or vaccine adjuvant(s) intended for mucosal immunization that is derived from whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, synthetic, cloned or recombinantly expressed, that consists of nucleotide sequences, proteins or other antigenic determinants capable of producing humoral or cellular-mediated immunity in humans or animals, and wherein the suppository is comprised of a suitable base that liquefies or becomes water miscible at body temperature in order to deliver vaccine components and/or vaccine adjuvant components to

the urogenital or anorectal mucosa so as to cause or enhance the development of a desired immune response.

Background of the Invention

Viral and microbial pathogens transmitted through or originating from exposure of the urogenital or anorectal epithelium or mucosa are a major problem in medicine. Urogenital and anorectal structures and systemic tissues beyond may be affected. Such infectious disease can result from mucosal exposure during sexual contact or other contact or from opportunistic growth of the urogenital or anorectal flora.

A tendency for recurrence, reinfection and chronic progression is characteristic of many urogenital or anorectal tract infections. Viral or microbial adherence to the mucosal epithelium is frequently a key precondition for the colonization or infection of these tissues. *In-vitro* studies have shown that the adherence phenomenon is often accomplished via the pili of bacteria or other outer membrane constituents of infecting viruses or microbes. Such adherence can be prevented by the development of antibodies and/or enhancement of cell-mediated immunity against antigenic components of the invading organisms, which include viruses, bacteria, protozoa, fungi and the like.

Bacteria and viruses are the most frequent causative agents of genitourinary or anorectal tract infections. The genitourinary/anorectal tracts can also be infected by other microorganisms, such as protozoa, fungi and the like. Recurrence and chronicity are characteristic of many genintourinary/anorectal tract infections. Recurrence may be due to either relapse or reinfection.

In spite of a great deal of progress in the treatment of infectious disease, the morbidity and mortality of genitourinary/anorectal tract infections remains unchanged. The reasons for this are myriad and depend on the host susceptibility, heightened sexual exposure and on viral or microbial factors.

Recurrences of infections with a previously infecting organism may result from inadequacy of the treatment administered because of incorrect choice of medicine, emergence of resistance strains, insufficient treatment duration, insufficient concentration of chemotherapeutic agents, the existence of bacterial L-forms, and persistence or survival of viral or microbes in urinary calculi or epithelium of the vaginal or anorectal mucosa and surrounding tissues. Recurrent urogenital/anorectal infections can be reinfections with different strains of organisms responsible for prior infections and generally having a greater capacity to adhere to the epithelial cells of the vagina, urethra or rectum. The reinfecting bacteria can originate in the intestinal flora. Frequently, viruses and chlamydia pathogens may lay dormant in epithelial cells and revert to an active state through mechanisms not fully understood.

The composition of the urogenital or anorectal flora may be altered by chemotherapeutic agents that are used in the treatment and prophylaxis of genitourinary or intestinal infections. The flora frequently develop antibiotic resistance and cause a reinfection or primary opportunistic infection. Such infections may be a consequence of the eradication of normal, harmless flora, such as lactobacilli, allowing other pathogenic microbes, resistant to the antibiotics, to flourish.

Studies have revealed that low levels of secretory IgA (sIgA) in urine indicate a defective local immune response of the urinary tract and favor urogenital tract infections. An

important property of sIgA is the prevention of interaction of bacterial pili or outer membrane constituents of viruses or other microbes with the specific receptors found on the epithelium of the vaginal/anorectal mucosa or urinary tract. Pili-mediated adhesiveness is an important virulence factor of the bacteria involved. In the case of viruses and non-piliated microbes, other outer membrane constituents are involved in host-attachment phenomena, prior to propagation to infection. For the defense against infection it is important to reduce the adhesion of the pathogens to the epithelium or to prevent the attachment of the pathogen altogether.

Normally, the host organism forms specific local antibodies against the invading bacteria and secretes these antibodies as sIgA. In patients with persisting or frequently relapsing urinary tract infections this natural mechanism of local immunological infection defense is apparently disturbed. Therefore, enhancement of immune defense is a rational means of eliminating the cause of recurrent urinary tract infections.

A vaccination strategy that stimulates the production of antibodies to a spectrum of antigens that are present in several types of pathogens is desirable. Vaccination of the urogenital or anorectal epithelium with nucleic acids encoding specific proteins involved in pathogen-host attachment phenomena presents a novel method of stimulating cell-mediated immunity.

Previously, vaccines against urogenital infections have been administered parenterally or orally and have resulted in enhanced resistance to urogenital infections. However, patients suffer from side effects such as malaise, fever, and muscle soreness. Oral vaccines are subject to the destructive influences of gastric acidity and digestive enzymes. A necessary retention at a local surface for extended transmucosal contact may be difficult to achieve. Prior art concerning mucosal vaccination through the vaginal route using whole cell lysates has taught enhanced resistance to

recurrent infection, but there is no mention of transmucosal immunization by the anorectal route and the production of transmucosal immunity against local infection at the site of delivery system target. No specifically therapeutic local immune response to a delivery system is presented. The efficacy presented is confined to non-specific vaccine materials that present a complex potential to produce complex reactions by poorly understood mechanisms.

In an attempt to overcome the defects associated with parenteral and oral administrations of vaccines or in using vaginally-delivered vaccines comprised of fractionated or whole cell extracts, an intravaginal or intrarectal mucosal vaccine delivery system against infections is proposed wherein the vaccine is comprised of purified antigenic determinants capable of stimulating an immune response to pathogenic factors involved in attachment and disease. Administering a vaccine against urogenital or anorectal infections intravaginally or intrarectally is that there is a mucosal immune system wherein antigens are absorbed through mucosal surfaces and processed by specialized local lymphoid tissues, after which antibodies are secreted onto local mucosal surfaces. In the case of nucleotide vaccines, epithelial cells of the mucosa express the proteins to the cell surface promoting cellular-mediated immune responses. As discussed above, in the genitourinary tract, temporary or partial deficiencies in local vaginal or urinary antibodies are an important factor in the heightened susceptibility to urogenital infections shown in some women. Immunization via the mucosal surfaces within the genitourinary tract is preferable to parental or oral routes as it has been discovered that vaccination via the intravaginal surface creates a secretory immune response in the urogenital tract. With nucleotide vaccines, such vaccination stimulates specific cellular-mediated immune responses.

Advances in the identification of specific pathogenic factors involved in infection attachment and propagation, the elucidation of the mucosal immune system and the ability of the mucosal tissue to participate in cellular-mediated immune response via nucleotide vaccination suggest that vaccination of the genitourinary/anorectal tract by a transvaginal or anal route is preferable to oral or parenteral immunization. The specific method of vaginal or rectal immunization may actually resolve infection before disease ensues, preventing pathogen attachment or neutralizing toxins prior to pathogen and host interaction.

For instance, in the past, urinary tract infections vaccines were administered vaginally in the form of a liquid vaccine. Several problems were associated with the intravaginal administration of liquid urinary tract infections vaccine. The major problem encountered was that the liquid vaccine flowed out of the vagina soon after insertion. This severely limits the amount of time that the liquid antigens are in contact with the mucosal surface of the vagina, decreasing the effectiveness of the vaccine. The antigens need sufficient contact with the vaginal mucous membrane to elicit a secretory immunoglobin response. Patients receiving the vaccination were required to lie in a supine position for an extended time after receiving the vaccine to prevent the vaccine from immediately flowing out of the vagina. However, often the vaccine still leaked out of the vagina following the period of time in the supine position, limiting the effectiveness of the vaccine. In addition, the requirement that patients lie in a supine position for an extended time after receiving the vaccine, is a burden on the patient. Patients may receive several vaccinations over the course of treatment and the patients must spend a considerable amount of time after each vaccination immobile.

USSN 08/923,813 entitled Vaginal Suppository Vaccine For Urogenital Infections was filed 9/4/97 and allowed. This application is owned by assignee herein and relates to a suppository based vaccine delivery system for immunizing against urogenital infectious diseases in humans.

It is apparent that improvements are necessary in optimizing vaccine delivery to the urogenital mucosa for effective prophylaxis against urogenital infectious diseases. Further, it is desirable to have a rectally-administered vaccine for effective prophylaxis against rectal tract infections involving transmission through the anorectal tract.

The subject invention overcomes the above limitations and others, and teaches a suppository-based vaccine delivery system for prophylaxis against urogenital and anorectal tract infectious diseases, such as bacterial, protozoal, fungi, viral infections and the like, using fractionated, whole cell or purified protein, nucleic acid or lipid constituents, whether native, mutated, synthetic, cloned or recombinantly expressed, of urogenital/anorectal pathogens that stimulate the generation of humoral or cellular-mediated immune response.

Summary of the Invention

According to the present invention, there is provided an intravaginally or intrarectally administered suppository based vaccine delivery system for prophylaxis against urogenital or anorectal localized or transmitted infectious diseases.

Further according to the present invention, there is provided a suppository based vaccine delivery system for the prophylaxis against or treatment of urogenitally or rectally transmitted or localized infectious diseases, such as bacterial, protozoal, fungal or viral infections

wherein the vaccine or vaccine adjuvant is in contact with the vaginal or anorectal mucous membrane for a sufficient period of time to enhance the immune response.

Still further according to the present invention, there is provided a suppository based vaccine delivery system for the prophylaxis against or treatment of urogenitally or rectally transmitted or localized infectious diseases, such as bacterial, protozoal, fungal or viral infections, wherein the vaccine or vaccine adjuvant is easily administered, does not require the patient to lie in a supine position for an extended period of time after receiving the vaccination, and is suitably administered by the patient for primary and routine booster requirements.

Still further according to the present invention, there is provided a suppository based vaccine delivery system for prophylaxis against urogenitally or rectally transmitted or localized infectious diseases, such as bacterial, protozoal, fungal or viral infections in humans or animals, said suppository comprising: a vaccine or vaccine adjuvant containing whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, synthetic, cloned or recombinantly expressed, that consists of nucleic acids, proteins, lipids or other antigenic determinants capable of producing humoral- or cellular-mediated immunity in humans or animals, wherein the suppository is comprised of a suitable base that liquefies or becomes water miscible at body temperature in order to deliver vaccine components to the urogenital or anorectal mucosa; wherein the suppository is adapted to be inserted vaginally or rectally so as to allow the suppository to be in contact with mucous membrane to facilitate transfer of vaccine or vaccine adjuvant material therethrough.

An advantage of the present invention is the provision of a suppository based vaccine delivery system for the prophylaxis against or treatment of urogenital and/or rectally transmitted or

localized infectious diseases, such as viral or other pathogenic microbial infections, wherein the vaccine or vaccine adjuvant is in contact with the vaginal or rectal mucous membrane for a sufficient period of time to enhance the immune response.

Another advantage of the present invention is the provision of a suppository based vaccine delivery system wherein humoral- and/or cell-mediated stimulation from mucosal vaccination allows immune responses to specifically keep viral or microbial shedding or colonization from occurring or recurring, or prohibiting pathogen-host attachment instead of fighting the infection after it has colonized or has propagated.

Another advantage of the present invention is the provision of a suppository based vaccine delivery system wherein the suppository can be easily manufactured to allow incorporation of vaccine or vaccine adjuvant(s) with preservatives, such as thimersal; is a solid at or below room temperature for structure and to allow ease of insertion; and becomes liquified or water-miscible at body temperature so as to allow its components to enhance an immune response.

Another advantage of the present invention is the provision of a suppository based vaccine delivery system for the prophylaxis against urogenitally or rectally transmitted or localized infectious diseases, such as viral or other pathogenic microorganism infections, wherein the vaccine is easily administered, and does not require the patient to be in a supine position for an extended period of time after receiving the vaccination.

Another advantage of the present invention is the provision of a suppository based vaccine delivery system wherein the vaccine can be readily self-administered by the patient.

Another advantage of the present invention is the provision of a suppository based vaccine delivery system wherein the administration of the vaccine is relatively painless.

Yet another advantage of the present invention is the provision of a suppository based vaccine delivery system wherein the patient may self-administer booster vaccinations periodically. Still other advantages of the invention will become apparent to those skilled in the art upon a reading and understanding of the following detailed description, and appended claims.

Detailed Description of the Preferred Embodiment

This invention is directed to a suppository based vaccine delivery system for immunizing against infectious disease in humans and animals and a method for treating the same. More particularly, this invention is directed to a suppository based vaccine delivery system for the prophylaxis against or treatment of urogenitally and anorectally localized or transmitted infectious diseases, such as from viral or other pathogenic microbial infections including but not limited to bacteria, protozoans, fungi and the like. The suppository based vaccine delivery system comprises a vaccine and/or vaccine adjuvant(s) comprising pathogenic microbial or viral antigenic constituents and optionally a preservative and optionally a buffer; wherein the suppository is adapted to be inserted into a bodily orifice of a human or animal so as to allow the vaccine and/or vaccine adjuvant to come in contact with the mucosal tissue of the bodily orifice to facilitate transfer of the suppository material therethrough.

The suppository comprises a vaccine and/or vaccine adjuvant(s) comprising fractionated or whole cell or purified cellular constituents whether native, mutated, synthetic, cloned or recombinantly-expressed pathogenic microbial or viral protein lipids or nucleic acid constituents that are capable of stimulating humoral- or cellular-mediated immune responses against which the pathogens or constituents correspond.

The suppository comprises a vaccine and/or vaccine adjuvant(s) that is prepared by either purifying native pathogen constituents, by synthesis or recombinant expression of protein or genetic components of native pathogens or by purifying synthetic, mutated or cloned pathogen-derived nucleic acid sequences.

The suppository of the present invention comprises any suitable suppository base known in the art. More particularly, the suppository base comprises material that is solid or semi-solid at or below room temperature but liquefies or becomes water-miscible at body temperature. The suppository base includes but is not limited to polyethylene glycol, triglycerides, fatty acids, fatty alcohols, glycerin and the like. Preferably the suppository base is polyethylene glycol. The suppository base optionally includes emulsifying agents such as polysorbate, gelatin, methylcellulose, alginic acid, sodium lauryl sulfate, and the like.

The suppository base is present in the delivery system in any suitable amount so as to allow the incorporation of the vaccine or vaccine adjuvant(s) in a solid or semi-solid form so that the structural integrity is maintained or that insertion into a body orifice can be easily performed. When inserted, the suppository base liquefies or becomes water-miscible at body temperature so as to allow the vaccine and/or vaccine adjuvant components to become in contact with the mucous membrane for a sufficient period of time to enhance the immune response. The weight percent of the suppository base is dependent upon the size of the bodily orifice of the human and/or the animal, the dosage of vaccine and/or vaccine adjuvant(s) necessary to elicit an immune response and its physiochemical characteristics that allow it to remain solid at or below room temperature. The suppository comprises from about 50% to greater than 99%, preferably about 75% to greater than 99% by weight of the suppository base. Preferably the suppository comprises about 75% to about

98% by weight polyethylene glycol. Preferably the suppository comprises about 2% to about 25% by weight polysorbate. The suppository base has a molecular weight in the range of about 400 to about 5000, preferably about 950 to about 3700. In a more preferred embodiment, the polyethylene glycol suppository base is comprised of about 39% by weight of polyethylene glycol having a molecular weight of about (3000) and about 59% by weight of polyethylene glycol having a molecular weight of about 400. A suitable commercially available polyethylene glycol suppository base is POLYBASE, available from Paddock Laboratories, Inc.

The suppository base optionally includes either or both of a preservative(s) and a buffer(s). The preservative is selected from the group consisting of thimersal, benzoic acid, benzoic acid derivatives, benzylkonium, benzylkonium chloride sulfites, quaternary ammonium salts, chlorobutanol and combinations thereof at concentrations ranging from about 0.01% to about 0.5%. The buffers are employed so that the pH of the suppository vaccine remains the same. The buffers used are those known in the art and include, but are not limited to citrate, phosphate, hepes (or their salts) and combinations thereof at a concentration in the range of about 5 milimolar to about 0.5 molar.

The suppository base confers a degree of miscibleness with the mucous membrane surfaces of the vagina or rectum, wherein suspended particles of the vaccine and/or vaccine adjuvant(s) are in contact with such mucous membrane surfaces for a sufficient amount of time to elicit a humoral- or cell-mediated immune response. The suppository base has an adjuvant effect that enhances the immune response by allowing the vaccine to facilitate contact time with the vaginal or anorectal tract mucous membranes, serving as a depot that slowly releases antigen, and by localizing and delivering antigens to immunocompetent cells. The suppository base possesses properties that allow the suppository to be molded in a desirable form and further function as a

structural necessity that keeps the suppository in its desired molded form at or below room temperature.

The suppository is allowed to harden in a suppository shell or a mold that forms the desired shape. The suppository is generally stored in the shell until used or is removed from the mold and repackaged. The suppository shell or mold is any shell or mold known in the art suitable for molding or packaging of the suppository. A suitable commercially available laminate suppository shell is a polyvinylchloride polyethylene laminate suppository shell available from Paddock Laboratories, Inc.

The suppository based vaccine delivery system of the present invention is prepared by general techniques known in the art. Typically, the suppository base vaccine delivery system is prepared under a sterile environment. The suppository base is heated in a sterile environment to a temperature in the range of its melting point to liquefy the base. The suppository base is heated for a time sufficient to liquefy it without degrading it.

The vaccine or vaccine adjuvant(s) comprising the whole or fractionated viral or other microbial pathogen, or their purified cellular constituents or derivatives, whether native, mutated, synthetic, cloned or recombinantly expressed, that consist of nucleic acids, proteins, lipids or other antigenic determinants capable of producing humoral-or cullular-mediated immunity is placed in a container containing the liquified suppository base. The vaccine and/or vaccine adjuvant(s) are stirred with the liquid suppository base until a homogeneous suspension is produced. A preservative or adjuvant is added and stirred until a homogeneous suspension is again attained. The suspension comprising the suppository base and the vaccine and/or vaccine adjuvant(s) and preservative is placed into individual laminate suppository shells. The suppository is then cooled at room

temperature to allow it to harden. The suppositories are then heat-sealed and stored at refrigerated temperature.

The suppository based vaccine delivery system according to the present invention when inserted into a bodily orifice and allowed to liquify or become water-miscible allows the vaccine to be in contact with the vaginal or rectal tract mucous membrane for a sufficient period of time to enhance the immune response. Further, the suppository based vaccine delivery system according to the present invention allows the incorporation of vaccine, vaccine adjuvant(s) and preservative and is easily administered, does not require the patient to lie in a supine position for an extended period of time after receiving the vaccination, is suitably administered by the patient, is painless, is amenable to routine booster vaccinations and allows a favorable method of antigen delivery to immunocompetent cells through the mucosa.

The present invention is further exemplified in the following example. The example illustrates the effectiveness of the suppository based vaccine delivery system of the present invention. It is understood that the example is only illustrative of preferred embodiments according to the present invention wherein the claims set forth the scope of the present invention.

EXAMPLE

In this example, the HSV-2 gD2 and its complementary DNA are used as representative vaccine candidates for mucosal immunization. This protein is specific to the herpes simplex-2 (HSV-2) virus and represents a major outer membrane constituent of the virus that is implicated in the host-attachment phenomena. Others have demonstrated that this protein is a candidate vaccine to prevent transmission or recurrence of HSV-2. This is based on its antigenicity

and, that following parenteral vaccination, it elicits satisfactory immune response based on protection against HSV-2 challenge in animal models. The DNA of HSV-2 gD2 is the cloned complementary DNA encoding this protein. Its use as a DNA vaccine is intended to stimulate the production of cellular-mediated immune response. Both the protein and cDNA is manufactured by Protein Express, Inc., Cincinnati, Ohio.

POLYBASE, a polyethylene glycol polysorbate suppository base manufactured by and available from Paddock Laboratories, Inc., in an amount sufficient to manufacture 50 two-gram suppositories, was heated in a sterile flask atop a magnetic stirrer/heater to a temperature of about 60°C for about one hour to liquefy the suppository base. Recombinant HSV gD2 protein and/or its complementary DNA, 500 micrograms each (enough to manufacture about 50 suppositories) was aseptically placed in the liquefied suppository base suppository. A sterile magnetic stir bar was placed in the flask, and the vaccine and suppository base were stirred for about 10 minutes at about 60°C in a temperature-controlled water bath to form a homogeneous suspension. Thimersal, as a preservative, was added to a final concentration of about 0.1% and stirred until a homogeneous suspension was achieved. The suspension comprised of the suppository base, the vaccine and the preservative was then placed into individual polyvinyl chloride-polyethylene laminate suppository shell using a sterile pipette. Approximately 2.0 ml of the suspension was placed into each shell.

The suppository base was cooled at a temperature of about 24°C for about 30 minutes to harden the suppository base. The top of each shell was heat-sealed and the suppositories were then stored at about 4°C. When used, the suppositories are removed from the shell and inserted vaginally or rectally.

While various embodiments of a suppository based vaccine delivery system for treating or prophylaxes against urogenitally and/or anorectally transmitted or localized infectious diseases and a method for treating or prophylaxes against urogenitally and/or anorectally transmitted infections in humans and animals have been disclosed, it should be understood that modifications and adaptations thereof will occur to persons skilled in the art. Other features and aspects of this invention will be appreciated by those skilled in the art upon reading and comprehending this disclosure. Such features, aspects, and variations and modifications of the reported results and examples are clearly within the scope of the invention where the invention is limited solely by the scope of the following claims.

Claims:

Having thus described the invention, it is now claimed:

1. A suppository based vaccine delivery system for prophylaxis against or treatment of urogenitally and anorectally transmitted infectious disease in humans and animals, said suppository comprising:

(a) a vaccine or vaccine adjuvant(s) selected from the group consisting of whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, mutated, synthetic, cloned or recombinantly-expressed and combinations thereof, that consists of nucleic acids, proteins, lipids, other antigenic determinants or combinations thereof capable of producing humoral- or cellular-mediated immunity in humans or animals; and

(b) a suppository base, selected from the group consisting of polyethylene glycol, polysorbate and combinations thereof;

wherein the suppository is adapted to be inserted into a bodily orifice of a human or animal so as to allow the suppository to be in contact with tissue of the bodily orifice to facilitate transfer of suppository material therethrough.

2. A suppository based vaccine delivery system for prophylaxis against urogenital tract infections in humans, said suppository comprising:

(a) a vaccine or vaccine adjuvant(s) selected from the group consisting of whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, mutated, synthetic, cloned or recombinantly-expressed and combinations thereof, that consists of nucleic acids, proteins, lipids, other antigenic determinants or combinations thereof capable of producing humoral or cellular-mediated immunity in humans; and

(b) a suppository base, selected from the group consisting of polyethylene glycol, polysorbate and combinations thereof;

wherein the suppository is adapted to be inserted vaginally so as to allow the suppository to be in contact with vaginal mucous membrane to facilitate transfer of suppository material therethrough.

3. A suppository based vaccine delivery system for prophylaxis against anorectally transmitted infectious disease in humans or animals, said suppository comprising:

(a) a vaccine or vaccine adjuvant(s) elected from the group consisting of whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, mutated, synthetic, cloned or recombinantly expressed and combinations thereof, that consists of nucleic acids, proteins, lipids, other antigenic determinants or combinations thereof capable of producing humoral or cellular-mediated immunity in humans or animals; and

(b) suppository base, selected from the group consisting of polyethylene glycol, polysorbate and combinations thereof;

wherein the suppository is adapted to be inserted rectally so as to allow the suppository to be in contact with the anorectal mucous membrane to facilitate transfer of vaccine or vaccine adjuvant material therethrough.

4. The suppository based vaccine delivery system of claim 1 wherein the vaccine content or vaccine adjuvant(s) is selected from the group consisting of whole cells, purified

constituents or is generated from known genetic information of urogenital or anorectally transmittable pathogens.

5. The suppository based vaccine delivery system of claim 1 wherein the vaccine or vaccine adjuvant(s) contents are present in the total amount of 10 to 1000 micrograms.

6. The suppository based vaccine delivery system of claim 1 wherein the suppository base is comprised of polyethylene glycol and polysorbate.

7. The suppository based vaccine delivery system of claim 6 wherein the polyethylene glycol suppository base is comprised of about 75% to about 98% by weight polyethylene glycol and about 2% to about 25% by weight polysorbate.

8. The suppository based vaccine delivery system of claim 6 wherein the polyethylene glycol has an average molecular weight of about 950 to about 3700.

9. The suppository based vaccine delivery system of claim 6 wherein the polyethylene glycol suppository base comprises from about 70% to greater than 99% by weight of the suppository.

10. The suppository based vaccine delivery system of claim 1 wherein the suppository is further comprised of a preservative selected from the group consisting of thimersal,

benzoic acid, benzylkonium, benzylkonium chloride, sulfites, quaternary ammonium salts, chlorobutanol and combinations thereof.

11. The suppository based vaccine delivery system of claim 10 wherein the suppository is further comprised of an emulsifying agent selected from the group consisting of gelatin, methyl cellulose, alginic acid, sodium lauryl sulfate and combinations thereof.

12. A suppository-based vaccine delivery system for prophylaxis against urogenital or anorectally transmitted infections in humans or animals, said suppository comprising:

(a) a vaccine or vaccine adjuvant(s) comprising purified, mutated, synthetic or genetically engineered constituents of known pathogens selected from the group consisting of urogenital pathogens, anorectally pathogens and combinations thereof; and

(b) a suppository base, selected from the group consisting of polyethylene glycol, polysorbate and combinations thereof;

wherein the polyethylene glycol suppository base is comprised of about 75% to about 98% by weight polyethylene glycol and about 2% to about 25% by weight polysorbate, wherein the polyethylene glycol has an average molecular weight of about 950 to about 3700, and wherein the polyethylene glycol suppository base comprises from about 70% to about 99% by weight of the suppository; wherein the suppository is adapted to be inserted vaginally or rectally so as to allow the suppository to be in contact with mucous membrane to facilitate transfer of vaccine or vaccine adjuvant(s) material therethrough.

13. A suppository-based vaccine delivery system for prophylaxis against genitourinary or anorectal tract infections in humans or animals, said suppository resulting from the mixture of:

(a) a vaccine or vaccine adjuvant selected from the group consisting of whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, mutated, synthetic, cloned or recombinantly expressed, that consists of nucleic acids, proteins, lipids, other antigenic determinants or combinations thereof capable of producing humoral or cellular-mediated immunity in humans or animals; and

(b) a suppository base, selected from the group consisting of polyethylene glycol, polysorbate and combinations thereof;

wherein the polyethylene glycol suppository base is comprised of about 75% to about 98% by weight polyethylene glycol and about 2% to about 25% by weight polysorbate, wherein the polyethylene glycol has an average molecular weight of about 750 to about 3700, and wherein the polyethylene glycol suppository base comprises from about 70% to greater than 99% by weight of the suppository base; wherein the suppository is adapted to be inserted vaginally or rectally so as to allow the suppository to be in contact with mucous membrane to facilitate transfer of vaccine or vaccine adjuvant(s) material therethrough.

14. A method for preventing urogenital or anorectal disease in humans or animals, said method comprising the steps of:

(a) inserting a suppository-based vaccine delivery system into a bodily orifice of a human, wherein said suppository comprises a vaccine or vaccine adjuvant(s) material

comprised of whole, fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, mutated, synthetic, cloned or recombinantly expressed, that consists of nucleic acids, proteins, other antigenic determinants or combinations thereof capable of producing humoral or cellular-mediated immunity in humans or animals; and

(b) contacting the suppository with mucosal tissue at and internal to the bodily orifice to facilitate transfer of the vaccine or vaccine adjuvant material therethrough and induce an immune response in the human.

15. The method of claim 14 wherein the protein or nucleic acid originate from the genetic constituents of pathogenic urogenital or anorectally transmissible viruses, other microbes or combination thereof.

16. The method of claim 14 wherein the amount of protein, nucleic acids, lipids, other antigenic determinants and combinations thereof are present in the total amount of about 10 to about 1000 micrograms.

17. The method of claim 14 wherein the polyethylene glycol suppository base is selected from the group consisting of polyethylene glycol, polysorbate and combination thereof.

18. The method of claim 17 wherein the polyethylene glycol suppository base is comprised of about 75% to about 98% by weight polyethylene glycol and about 2% to about 25% by weight polysorbate.

19. The method of claim 18 wherein the polyethylene glycol has an average molecular weight of about 750 to about 3700.

20. The method of claim 14 wherein the suppository base comprises from about 80% to greater than 99% by weight of the suppository base.

Abstract of the Disclosure

The invention is directed to a suppository based vaccine delivery system for immunizing against urogenital and anorectally transmitted infectious disease in humans and animals and a method for treating the same. More particularly, this invention is directed to a suppository based vaccine delivery system for the prophylaxis against or treatment of urogenital or anorectal transmitted infectious diseases, such as from viral or microbial pathogens. The suppository based delivery system comprises vaccine and/or vaccine adjuvant(s) comprised of whole or fractionated viral or other microbial pathogens, or their purified cellular constituents, whether native, mutated, synthetic, cloned or recombinantly expressed, that consists of nucleic acids, proteins, lipids or other antigenic determinants capable of producing humoral or cellular-mediated immunity in humans or animals; and a polyethylene glycol base; wherein the suppository is adapted to be inserted into a bodily orifice of a human or animal so as to allow the suppository to be in contact with tissue of the bodily orifice to facilitate transfer of vaccine or vaccine adjuvant(s) material therethrough.

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, DC 20231,
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Docket No.: 45061-8

DECLARATION FOR PATENT APPLICATION

As a below named inventor, we hereby declare that:

Our residence, post office address, and citizenship are as stated below next to our names.

We believe we are the original, first, and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

UROGENITAL OR ANORECTAL TRANSMUCOSAL VACCINE DELIVERY SYSTEM

the specification of which is attached hereto.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, § 119(a) - (d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

NONE

We hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States application(s) listed below:

NONE

We hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112. We acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

NONE

We hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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